53. (new) The composition of claim 19, which further comprises a pharmaceutically acceptable carrier.

54. (new) The composition of claim 19, further comprising an adjuvant.

55. (new) The composition of claim 19 wherein the adjuvant is selected from the group consisting of a pluronic tri-block copolymer, muramyl dipeptide, detoxified endotoxin, saponin, QS-21, and liposome.

## REMARKS

Claims 19-51 were pending. Claims 20, 21 and 32-51 were withdrawn from consideration as drawn to a non-elected invention and have now been cancelled without prejudice. Applicant reserves the right to pursue the subject matter of cancelled claims 20, 21 and 32-51 in a related application. New claims 52-55 have been added and are fully supported by the specification as filed. Specifically, support for new claim 52 can be found in the specification as filed at page 19, lines 19-21 and page 6, lines 27-29. Support for new claim 53 can be found in the specification as filed at page 26, lines 13-16. Support for new claim 54 can be found in the specification as filed at page 26, lines 16-17. Support for new claim 55 can be found in the specification as filed at page 26, lines 17-21. A copy of the pending claims upon entry of the above amendments is attached hereto as Exhibit A.

## THE INDEFINITENESS REJECTION SHOULD BE WITHDRAWN

Claim 24 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Examiner asserts that the term "low" in claim 24 is a "relative" term. October 22, 2002 Office Action at 3. Applicant respectfully disagrees and submits that "low pH" as used in claim 24 is definite.

As discussed in the Applicant's previous response, definiteness turns on whether one of skill in the relevant art would understand the bounds of a claim when read in light of the specification. *See Orthokinetic Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081 (Fed. Cir. 1986).

As a preliminary matter, while the term "low" by itself may in some instances be a relative term, Applicant respectfully points out that the term "low" as used in claim 24 was not intended to be read in isolation, but instead as part of the phrase "low pH".

Applicant asserts that low pH is not a term of degree and that it is a term of art which one of skill in the art reading claim 24, would understand to mean acidic pH. Applicant directs the Examiner's attention to the following references: Reference FX (made of record in the revised form PTO-1449 filed herewith, Huesca, M. *et al.*, 1996, Infection and Immunity 64(7): 2643-2648 "Acidic pH Changes Receptor Binding Specificity of *Helicobacter pylori*: a Binary Adhesion Model in which Surface Heat Shock (Stress) Proteins Mediate Sulfatide Recognition in Gastric Colonization"[1],); Reference FY (made of record in the revised form PTO-1449 filed herewith, Mellman, I. *et al.*, 1984, J. Cell Biology 98: 1163-1169 "Internalization and Rapid Recycling of Macrophage Fc Receptors Tagged with Monovalent Antireceptor Antibody: Possible Role of a Prelysosomal Compartment"); Reference FZ (made of record in the revised form PTO-1449 filed herewith, Reay, Philip A. *et al.*, 1992, EMBO J., 11(8):2829-39 "pH Dependence and Exchange of High and Low Responder Peptides Binding to a Class II MHC molecule"); and Reference GA (made of record in the revised form PTO-1449 filed herewith, Varga, M. *et al.*, 1990, J. Virology 64(9): 4217-4225 "Antibodies with Specificities against a Dispase-Produced 15-Kilodalton Hexon Fragment Neutralize Adenovirus Type 2 Infectivity").

[1] Even though Reference FX by Huesca post-dates the effective filing date of the application, Applicant submits that the reference evidences an understanding in the art as to the term "low pH" that has not changed since the filing date.

In Reference FX, a reference from the heat shock protein art, the terms acid pH and low pH are used interchangeably. In Reference FY, pH 4, low pH and acidic pH are used interchangeably. In Reference FZ, pH 5 and low pH are used interchangeably. In Reference GA, pH 5.0 and low pH are used interchangeably. A marked-up copy of each of the foregoing references, References FX-GA, is attached hereto as Exhibit B, in which instances of "acid pH", "low pH" and specific low pH values are underlined for the convenience of the Examiner.

Even assuming arguendo that "low pH" is a relative term, the Applicant submits that relativity alone is not sufficient to render the claim indefinite. Importantly, the mere fact that claim language contains a term of degree, which may not be precise, does not automatically render a claim indefinite under 35 U.S.C. § 112, second paragraph. *See* MPEP § 2173.05(b) and *Seattle Box Co. v. Industrial Crating and Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). Rather, a determination of definiteness, even when a term of degree is used, must turn on whether one of ordinary skill in the art, in view of the prior art and the status of the art, would be nevertheless reasonably apprised of the scope of the invention. *See* MPEP § 2173.05(b).

As evidenced by References FX-GA discussed above, the terms "acid pH" and "low pH" are used interchangeably in the art and one of skill in the art would be reasonably apprised of the scope of claim 24. Therefore the indefiniteness rejection is in error and should be withdrawn.

**THE WRITTEN DESCRIPTION REJECTION SHOULD BE WITHDRAWN**

Claims 19 and 22-31 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which, allegedly, is not described in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner understands that the claimed

invention is drawn to a pharmaceutical composition comprising a population of peptides derived from the separation of a stress protein and its associated peptide. However, while acknowledging that "the stress-protein-peptide complex can be determined and isolated" the Examiner concludes that "the claims as currently recited read on any protein fragment or polypeptide fragment that is derived from a tumor cell from which the complex was initially extracted." October 22, 2002 Office Action at 3-4. The Examiner further states that "One of skill in the art would not be able to determine with any certainty what the composition comprises because the polypeptide and or peptides themselves have not been adequately described." Office Action at 4. In particular, the Examiner asserts that because detailed information regarding the structure or amino acid sequence of the peptides has not been provided in the specification, there is a lack of written description of the peptides. Applicant respectfully submits that the Examiner is in error.

Preliminarily, Applicant reminds the Examiner that claims 19 and 22-31 are product-by-process claims. By definition, product-by-process claims recite a product or composition of matter (or its elements) by the process by which it is made, rather than by its structural or chemical characteristics. *See* MPEP § 2173.05(p).

A careful review of the rejected claims (claim 19, and dependent claims 22-31) reveals that they are indeed product-by-process claims, *i.e.*, they are product claims that define the claimed product in terms of the process by which it is made. In particular, the preamble of claim 19 sets forth a product, "a composition", by the process by which is it made, "a method comprising the steps of: purifying . . . ; releasing . . . and recovering . . .".

As such, Applicant disagrees with the Examiner's contention that the law requires that the specification provide "detailed information regarding structure or amino acid sequence of the peptide or peptides." Office Action at 4. The written description requirement simply serves to ensure that "the inventor had possession, as of the filing date of

the application relied on, of the specific subject matter later claimed by him." *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90,96 (CCPA 1976). Notably though, the manner in which "the specification accomplishes this [communication of possession] is not material." *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). Thus, an Applicant need not utilize any particular form of disclosure to describe subject matter claimed, if persons of ordinary skill in the art reading the specification are able to recognize that the inventor is in possession of what is claimed. Necessarily then, "[p]recisely how close the original description must come to comply with the description requirement of section 112 must be determined on a case-by-case basis." *Eiselstein v. Frank*, 52 F.3d 1035, 1039, 34 USPQ2d 1467, 1470 (Fed. Cir. 1990) (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991)).

The mere fact that a claim to a composition is couched in terms of the process by which said composition is made, is not enough to render the claim objectionable. Claims directed to a product-by-process are proper. MPEP § 2173.05(p) defines and explicitly approves the use of a product-by-process claim format. A "product-by-process claim, which is a product claim that defines the claimed product in terms of the process by which it is made, is proper." MPEP 2173.05(p). *In re Luck*, 476 F.2d 650, 177 USPQ 523 (CCPA 1973).

Furthermore, the Examiner contends that "because the specification has not described the structure or make-up of the peptides of the composition, [the composition] can be equivalent to any known composition wherein the composition comprises a peptide or protein fragment." Office Action at 4. To the extent that the Examiner is thereby raising a prior art concern, Applicant submits that such is unfounded. The population of peptides produced by the method specified in the claims is a new composition containing myriad different peptides that were bound to stress proteins in mammalian tumor cells. The claimed

composition comprising a recovered population of peptides is not in the prior art, and the Examiner has come forward with no evidence to the contrary.

In view of the foregoing, the outstanding rejection concerning lack of written description has been overcome. Accordingly, the Applicant requests that the Examiner reconsider and withdraw the rejection of claims 19 and 22-31.

**THE INDEFINITENESS REJECTION SHOULD BE WITHDRAWN**

Claims 19 and 22-31 stand rejected under 35 U.S.C. § 112, first paragraph as being indefinite. In particular, the Examiner asserts that one of skill in the art cannot envision what the peptide is, the structure or amino acid sequence, and therefore cannot determine the metes and bounds of the term. Applicant respectfully disagrees. The definition of peptide is clear to one of skill in the art. Applicant respectfully directs the Examiner's attention to the Reference GB, a dictionary definition of peptide (made of record in revised form PTO-1449 filed herewith, page 1391 of Dictionary of Scientific and Technical Terms, McGraw-Hill (1989)). Therein, peptide is defined as "A compound of 2 or more amino acids joined by peptide bonds." The Applicant respectfully submits that the metes and bounds of the term peptide would be clear to one of skill in the art. Moreover, as discussed above, claims 19 and 22-31 are product-by-process claims, and thus the claimed composition need not be described by structure or chemical characteristics, but, rather, can be described by the process by which it is made. The indefiniteness rejection should be reconsidered and withdrawn.

**THE ANTICIPATION REJECTION SHOULD BE WITHDRAWN**

Claim 19 is rejected under 35 U.S.C. §102(b) as being anticipated by Asano, T.J., *et al.*, 1993, Immunother. 14(4): 286-92 ("Asano"). Applicant respectfully disagrees and submits that Asano is not sufficient to render claim 19 anticipated.

As a preliminary matter, Applicant notes that only an abstract, not a full copy, of Asano was provided with the October 22, 2003 Office Action. Applicant submits herewith

a full copy of Asano as Reference GD, made of record in revised form PTO-1449 filed herewith, Asano, T.J., *et al.*, 1993, Immunother. 14(4): 286-92.

The legal standard for anticipation is one of strict identity. A claim is anticipated only if each and every element set forth in the claim is found in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 2 USPQ2d 1051 (Fed. Cir. 1987). In other words, there must be no difference between the claimed invention and the reference dislcosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). When examining a product-by-process claim for novelty, one looks to the final product of the claimed process, disregarding the process limitations. *In re Thrope*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted); *see also* MPEP 2113. As discussed below, the single peptide discussed in Asano cannot anticipate the product of the instant claims.

Asano describes the role of a novel immune modulator in monocyte chemotactic and activating factor (MCAF) expression in monocytes. In particular, Asano details the use of one specific immune modulator, L-MTP-PE, a liposome encapsulated MTP-PE. The structure of MTP-PE is established by Reference GC (made of record in the revised form PTO-1449 filed herewith, Mackova N. and Fedorocko, P., 2002, Physiol Res. 51:511-521 "Effect of Liposomal Muramyl Tripeptide Phosphatidyl-ethanolamine and Indomethacin on Hematopoietic Recovery in Irradiated Mice"). L-MTP-PE is a synthetic liposome-encapsulated muramyl tripeptide (N-acetylmuramyl-L-alanyl -D-isoglutaminyl-L-alanine) that is covalently linked to dipalmitoyl phosphatidylethanolamine. (*See* Reference GC, at page 512, column 2, "Reagents" section).

In contrast, the present invention relates to a population of naturally occurring peptides that are recovered from non-covalently complexed stress proteins. Moreover, the

recovered population of peptides encompassed by the claims comprises a highly complex and rich mixture of different kinds of peptides, *i.e.*, a plurality of peptides. *See* Reference CM, Li and Srivastava, Aug. 1993, EMBO J. 12(8): 3143-3151 "Tumor rejection antigen gp96/grp94 is an ATPase: Implications for protein folding and antigen presentation" (Figure 10 shows heterogenous peptides eluted from gp96 by C18 HPLC column); and Reference DT, Udono *et al.*, Oct. 1, 1993, J. Exp. Med. 178: 1391-1396 "Heat shock protein 70-associated peptides elicit specific cancer immunity" (Figure 4 shows diverse array of peptides with molecular mass between 1,000 and 5,000 daltons eluted from hsp70 complexes by C18 HPLC column) both made of record in revised form PTO-1449 filed on April 27, 2001).

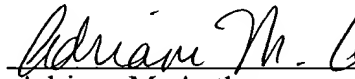
Applicant submits that Asano fails to teach every element of the claimed invention. Asano does not teach the claimed population of peptides. One peptide, *i.e.*, L-MTP-PE, is not the population of peptides recovered from stress proteins. Thus, Asano cannot anticipate the invention claimed herein. The Applicant respectfully requests that the anticipation rejection over Asano be reconsidered and withdrawn.

## CONCLUSION

The Applicant respectfully requests that the remarks of the present response be entered and made of record in the instant application. Claims 19 and 22-31 fully meet all the statutory requirements for patentability. Withdrawal of the Examiner's rejections and early allowance and action for issuance are respectfully requested.

Respectfully submitted,

Date March 21, 2003



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Enclosures

**EXHIBIT A**
**CLEAN VERSION OF PENDING CLAIMS**
**U.S. PATENT APPLICATION NO. 09/657,722**

19. A composition comprising a recovered population of peptides in admixture with a pharmaceutically acceptable non toxic carrier, wherein said recovered population of peptides is produced by a method comprising the steps of:

(a) purifying a population of stress protein-peptide complexes from mammalian tumor cells, wherein the stress protein is non covalently associated with the peptide in said complexes;

(b) releasing the peptides from said population of complexes to produce a released population of peptides; and

(c) recovering the released population of peptides.

22. The composition of claim 19 further comprising a cytokine.

23. The composition of claim 22 wherein said cytokine is selected from the group consisting of IL-1$\alpha$, IL-1$\beta$, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IFN$\alpha$, IFN$\beta$, IFN$\gamma$, TNF$\propto$, TNF$\beta$, G-CSF, GM-CSF, and TGF-$\beta$.

24. The composition of claim 19 wherein the peptides are released from said population of complexes by a method comprising placing said population of complexes in the presence of adenosine triphosphate, low pH, or both.

25. The composition of claim 19, wherein said mammalian tumor cells are human cells.

26. The composition of claim 19 wherein said mammalian tumor cells are from a tumor selected from the group consisting of melanocarcinoma, hepatocarcinoma, and renal cell carcinoma.

27. The composition of claim 19 wherein said tumor cells are from a metastasis.

28. The composition of claim 19, wherein said tumor cells have been proliferated in vivo.

29. The composition of claim 19, wherein said tumor cells have been proliferated in vitro.

30. The composition of claim 19, wherein the stress protein is a member of a stress protein family selected from the group consisting of hsp60, hsp70, and hsp90.

31. The composition of claim 19, wherein the stress protein is gp96.

52. The composition of claim 19, wherein the stress protein is hsp70.

53. The composition of claim 19, which further comprises a pharmaceutically acceptable carrier.

54. The composition of claim 19, further comprising an adjuvant.

55. (new) The composition of claim 19 wherein the adjuvant is selected from the group consisting of a pluronic tri-block copolymer, muramyl dipeptide, detoxified endotoxin, saponin, QS-21, and liposome.

**EXHIBIT B**
**MARKED-UP VERSION OF LOW pH REFERENCES**
**REFERENCES FX-GA**
**U.S. PATENT APPLICATION NO. 09/657,722**